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RESEARCH STUDY INFORMATION & DEFERRED ASSENT FORM

COVID-19: Pandemic infection is either suspected or proven

STUDY TITLE: Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community- Acquired Pneumonia (REMAP-CAP*).*

NAME OF PRINCIPAL INVESTIGATOR: Prof. Alistair Nichol

Your relative has been included in a research study.
This is because they have a condition called pneumonia which is an infection of the lungs caused by a new Coronavirus. The disease is called COVID-19.

Most patients with pneumonia due to COVID-19 who are being treated in an Intensive Care Unit will receive many different treatments, as many as 20 or 30 different treatments, that act together to treat both the infection and its effects on the body. For this research project:

- Several treatments may be tested, at the same time, in the same patient.
- We will tell you if the participant is not eligible for all options that are tested in the study.
- You can choose the parts of the study the participant participates in.
- Because COVID-19 is a new disease, doctors don't already know which treatments work best and the side effects of some treatment options.
- The study looks at its results as it goes and uses the results so that new patients in the study have a better chance of getting better treatments.
- The different treatment options are tested to tell which are the best. The study only tests options where it is not known which treatments are best.

About this Information Sheet and Consent Form

This Information Sheet/Assent Form tells you about the research project. It explains the treatments involved and how it is determined which treatments the participant will receive. Knowing what is involved will help you decide if you want your relative to continue to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not your relative can continue to take part, you might want to talk about it with a relative, friend or the participant's local doctor.

Participation in this research is voluntary. If you don't wish for your relative to continue to take part, they don't have to. They will receive the best possible care whether or not they take part.

If you decide you want your relative to continue to take part in the research project, you will be asked to sign the assent section. By signing it you are telling us that you:

- Understand what you have read
- Consent to your relative continuing to take part in the research project
- Consent to your relative having the tests and treatments that are described, so long as their doctor thinks they are appropriate
- Consent to the use of your relatives personal and health information as described.

You will be given a copy of this Information and Assent Form to keep.

WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of this research is to improve survival and recovery for patients with pneumonia.

We understand that your relative being a patient with pneumonia can be very concerning. The doctors and the team associated with this research project are dedicated to giving the participant the best possible treatments.

Patients with pneumonia receive many different treatment options as part of standard care but doctors aren't always sure which of these treatments are best.

All of the medications used in this research project are already commercially available. Many of these have been suggested to be of benefit and have been used to treat patients with COVID-19 pneumonia. However, clinicians are unsure if they are truly effective against COVID-19 infection. This study is designed to resolve that uncertainty.

1.COVID-19 – use of antiviral agents. There are some antiviral medicines that may work against COVID-19. Doctors don't know if any of them work or what side effects they may have. At this site, this project evaluates:

Lopinavir/ritonavir (also known as Kaletra)

OR

Hydroxychloroquine

OR

Hydroxychloroquine and Lopinavir/ritonavir (also known as Kaletra)

OR

No antiviral agent that is intended to be active against COVID-19

The doctors in this ICU have chosen these options because they don't know which option is best. Treatment guidelines and recommendations from the World Health Organisation is that, for COVID-19, treatments with unknown benefit should only be administered in a clinical trial. The use of antivirals is not a usual treatment for COVID-19, so this evaluation is a "new treatment".

2.COVID-19 - use of immune modulation. There are some medicines that may work against COVID-19 by affecting the patient's immune system. Doctors don't know if any of them work or what side effects they may have. At this site, this project evaluates:

Interferon-beta 1a

Anakinra

No agent that is intended to modulate the immune response

The doctors in this ICU have chosen these options because they don't know which option is best. Treatment guidelines and recommendations from the World Health Organisation is that, for COVID-19, treatments with unknown benefit should only be administered in a clinical trial. The use of immune modulation is not a usual treatment for COVID-19, so this evaluation is a "new treatment".

3.Whether to use hydrocortisone. Hydrocortisone is an anti-inflammatory medication. Some doctors believe it helps reduce inflammation in the lungs and elsewhere in the body, and that this helps the body to recover. Other doctors disagree and don't use the medicine, and others use the medicine only when a patient is very unwell (is in "septic shock"). At this site, this project evaluates:

No corticosteroids

A fixed duration of treatment with hydrocortisone

Hydrocortisone given only when the patient is in "septic shock"

The doctors in this ICU don't know which treatment is best but believe all options are safe and reasonable. Therefore, the choice of whether to use hydrocortisone or not is comparing different types of "standard care".

4.Choice of antibiotic. All patients who doctors think have pneumonia are given antibiotics, but doctors give different antibiotics. At this site, this project evaluates the following antibiotics:

Ceftriaxone and a macrolide

Amoxicillin-clavulanate and a macrolide

The doctors in this ICU have chosen to have these options available in the study because all of these options are known or believed to be safe and effective. If your relative is not in the study, it is very likely that the doctors would have treated them with one of these options. However, it is not known which option is best. The choice of antibiotic evaluates different types of "standard care". The doctors in this ICU will be asked to consider whether the above antibiotics are appropriate for your relative's individual medical presentation.

5.Duration of macrolide treatment. The medicine, Clarithromycin or Azithromycin , is a macrolide antibiotic that also has some anti-inflammatory actions. Most doctors give

Clarithromycin or Azithromycin to most patients with pneumonia but stop after a few days. However, if it's stopped early the patient may not benefit from it's anti-inflammatory effect. In this research project, stopping Clarithromycin or Azithromycin after a few days will be compared with continuing it for up to 14 days. The longer course of Clarithromycin or Azithromycin is not a usual treatment, so this evaluation is a "new treatment".

6.Use of influenza antiviral medications. When a patient has pneumonia caused by an influenza virus, some doctors will prescribe a drug called Oseltamivir, an antiviral medication. Some doctors do not routinely use Oseltamivir, and those who do may prescribe it for different lengths of time. At this site, this project evaluates:

Oseltamivir for five days

Oseltamivir for ten days

The doctors in this ICU have selected these options because they do not know which of them is best, but believe that all of these options are safe and effective. Therefore, these options are different types of "standard care". The participant will only receive these treatments if they have pneumonia that is believed or known to be caused by Influenza.

WHY HAVE I BEEN APPROACHED?

We would like to explain to you why your relative was included in this study and ask your permission for them to continue at this time, as they are unable to consent for themselves.

Normally patients are included in medical research studies only if they agree to be included in the study and understand what is involved ("Informed Consent"). In medical research into conditions where the patient is critically ill, the patient is often unable to discuss what is involved at that time.

WHY HAS MY RELATIVE BEEN CHOSEN?

Your relative has been enrolled in this study. They have a condition called pneumonia which is an infection of the lungs caused by a new Coronavirus called COVID-19, and they are eligible to receive treatments as part of this study to see if they will be effective against their condition.

Your relative has been enrolled as a participant in this research project without obtaining their consent in advance due to their condition at the time. The Health Research Consent Declaration Committee has approved deferred assent from a relative for enrolment into this study.

The following combinations of treatments will be used in this hospital:

a) Ceftriaxone + 3-5 days Clarithromycin or Azithromycin

b) Ceftriaxone + up to 14 days Clarithromycin or Azithromycin

c) Amoxicillin-clavulanate + 3 -5 days Clarithromycin or Azithromycin

d) Amoxicillin-clavulanate + up to 14 days Clarithromycin or Azyithromycin

Combined with
e) either hydrocortisone or no hydrocortisone or hydrocortisone given only when the patient is in "septic shock"

f) Oseltamivir for 5 days or 10 days
g) Lopinavir/ritonavir (also known as Kaletra) or hydroxychloroquine or hydroxychloroquine and lopinavir/ritonavir or no antiviral agent that is intended to be active against COVID-19

h) Interferon-beta 1a or Anakinra or No agent that is intended to modulate the immune response

The antibiotics and hydrocortisone treatments are being administered intravenously.
The antiviral is administered orally.

HOW WILL THE STUDY BE PERFORMED?

It concerns a randomised study. Randomisation is a process that can be compared to tossing a coin. Every participant has a 50% chance of receiving either of the two treatment options. In addition, this study uses an adaptive study design. This means that based on the study results, the chance of receiving one of the treatment options may change, in favour of the more promising treatment.

It is important for the treatment of your relative's pneumonia that the antibiotics and supportive treatment selected are started as soon as possible. Therefore, these medicines are already assigned ("randomised") to your relative once they were admitted to the ICU. If you do not wish to give your assent for their continued participation in the study, their data will not be collected. The treatment started previously will in principle be continued and will be adjusted if the treating doctor considers this necessary.

If you give your assent for your relative's continued participation in the study after the discussion, their pneumonia will continue to be treated with the medication started previously, and this treatment will be adjusted if the treating doctor considers this necessary. In addition, data such as Temperature, Blood Pressure, Heart Rate and ventilator readings will be collected

about your relative during the remainder of their stay in Intensive Care.

The data collected for the study is already being collected as part of your relative's day- to-day medical care and no extra tests will be performed.

ARE THERE ANY RISKS OR BENEFITS FROM MY PARTICIPATION?

Medical treatments often cause side effects. The risks from side effects are similar if you choose your relative not to be in the study. The doctor will know what treatment they are receiving at all times, and will be looking out for side effects. As these are all commonly used drugs, the doctors and nurses who will be caring for your relative while in the ICU are trained to recognise the risks associated with them. If side effects occur and the doctor thinks it's best to stop that treatment that is what will happen.
We cannot guarantee or promise that the participant will receive any benefits from this research.

WHAT ARE THE EXPECTED SIDE EFFECTS?

All medicines have side effects. As your relative is in intensive care and will be receiving various medicines, it is possible that they will experience side effects . The medication is also necessary, however, and can be life saving. It is not easy to determine which medicine is causing side effects. The medication in this study can cause side effects, from very minor to very serious. The doctor will weigh the side effects up against the advantages of the medication. The doctor is convinced that this treatment is more important than the possible side effects that may occur. Whether or not the treatment in this study is still in your relative's interest will be determined again every day. The medication will be adjusted if your relative's doctor thinks this is necessary. The list of possible side effects can be found in annex 2.

WHAT HAPPENS IF YOUR RELATIVE DOES NOT TAKE PART IN THIS STUDY?

Whether or not you want your relative to continue to take part in the study is your decision. Participation is entirely voluntary. If you decide against participation, you will not need to do anything else. You will not need to sign anything. You will not need to give a reason for not taking part either. As a patient they will still receive the treatment they would otherwise receive. If you decide on behalf of your relative for them to continue to participate, you can always change your mind and withdraw from the study, even once the study has already started. Furthermore, the doctor may decide to discontinue participation in the study if they believe it is no longer in your relative's best interest to participate. Moreover, inspection authorities have the right to interrupt or discontinue the study at any time.

FOLLOWING DISCHARGE FROM HOSPITAL

Your relative will be contacted by a trained research co-ordinator by telephone at approximately 6 months after participation started in this research study to collect information on their recovery.

The trained research coordinator will collect information on your relative's quality of life. It is expected this phone call will take about 10 minutes. In order for this phone call to take place, we will ask you and/or your relative to supply contact phone numbers for this phone call.

CONFIDENTIALITY

Please find the details on confidentiality in Annex 1.

COMPENSATION

Your doctors are adequately insured by virtue of their participation in the Clinical Indemnity Scheme.

WHO IS ORGANISING AND FUNDING THIS RESEARCH?

This study is organised and funded by the European Commission FP7 program, and this study has been endorsed by the Irish Critical Care Trials Group.
The cost of some treatments for immune modulation for COVID-19 may be covered by pharmaceutical companies that make these products. These pharmaceutical companies have no involvement in the design, analysis, or reporting of results from the trial.

HAS THIS STUDY BEEN REVIEWED BY AN ETHICS COMMITTEE?

The St. Vincent's Healthcare Group, Ethics and Medical Research Committee have reviewed and approved this study.

CONTACT DETAILS

If you need further information,please contact Professor Alistair Nichol Alistair.nichol@ucd.ie
Phone No: 01 7165826

Research Participants Rights
If you have any questions about your relative's rights as a research participant,then you may contact the Hospitals Quality & Patient Safety Department 01 2214013

Annex 1 :CONFIDENTIALITY AND DATA PRIVACY

Your relative's identity will remain confidential. A study number will identify them (pseudo anonymised).Your relative's name will not be published or disclosed to anyone. No identifying material will be used in any reports of this study. Records for the study will be kept in a secure filing cabinet in a secure office located at St Vincent's University Hospital. Research Coordinators and the Investigator listed on the front of this assent form will have access to your relative's study data. Your relative's health records, and any information obtained during the study are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives from St Vincent's University Hospital or as required by the law. By the signing of the assent section, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

Would the information obtained in this study be kept confidential?

University Medical Center Utrecht is the Sponsor for this study (the institution who is responsible for oversight of the study). We will be using information from your relatives' medical records in order to undertake this study. If you withdraw your relative from the study, pseudsnonymised data recorded up to the point of withdrawal will be included in the study analysis unless you request otherwise.

PROCESSING OF YOUR RELATIVES PERSONAL DATA

St Vincent's University Hospital will process your relatives personal data for the following purposes on the basis of your consent:

Personal data	Purpose of processing
1. **Identification e.g. name, address, DOB (please note this and subsequent information will be anonymised/coded once leaving SVUH)**	1. **(a)Originally captured as part of medical care** **(b) used for purpose of carrying out research**
2. **Test results**	2. **Clinical care, safety measures, research outcomes**
3. **Clinical History (not identifiable)**	3. **PMH relevant to study outcomes**
4. **Questionnaires**	4. **PROMS required to measure response to treatment**

Where does St. Vincent's University Hospital obtain my relatives personal data from?

Most of the personal data we process is obtained from you directly but we also obtain personal data about you relative from their

- medical notes,
- lab test results,
- x-ray results,

SHARING OF PERSONAL DATA

Your relatives personal data will in particular be shared with:

**NOTE: These parties will either be acting as Processors of your information as part of this research study e.g. CROs, non-SVUH employees supporting research process or Controllers in their own right.*

Person/Company/institute	**Requirement for sharing**
Sponsor's monitor (UMC Utrecht)	Data quality control

Service Providers
We use third party service providers who provide services including financial services, occupational health and IT services. In providing the services, your relatives personal data will, where applicable, be processed by the service provider on our behalf.

We will check any third party that we use to ensure that they can provide sufficient guarantees regarding the confidentiality and security of their personal data. We will have written contracts with them which provide assurances regarding the protections that they will give to your relatives personal data and their compliance with our data security standards and international transfer restrictions.

Disclosures to Third Parties

In certain circumstances, we share and/or are obliged to share your relatives personal data with third parties outside St. Vincent's Hospital, for the purposes described above and in accordance with Data Protection Legislation.

These third parties include but are not limited to:

- the Health Products Regulatory Authority;
- the Health Service Executive;
- the Joint Commission International;
- relevant industry bodies;
- external professional advisors; and
- others, where it is permitted by law, or where we have your consent.

To assist with rapid generation of knowledge in the COVID-19 pandemic, we will share de-identified research data and findings relevant to the novel coronavirus (COVID-19) outbreak with public health and research communities and the World Health Organisation (WHO).

TRANSFERS OUTSIDE THE EUROPEAN ECONOMIC AREA

Your relatives personal information will be transferred, stored and processed in Australia which is outside the European Economic Area ("EEA"). For transfers of your relatives personal data. We have put in place adequate safeguards with respect to the protection of your privacy, fundamental rights and freedoms, and the exercise of your rights, e.g. we establish an adequate level of data protection through EU Standard Contractual Clauses based on the EU commission's model clauses.

STORAGE OF PERSONAL DATA

We will keep your relatives personal data for 15 years This may mean that some Information is held for longer than other information.

Storage and use of data for other research
Your relatives data may also be useful for other scientific studies in the field of lung infections after this study has finished. Their data will be stored for 15 years in a data bank for this purpose. You can indicate on the informed consent form whether or not you accept this. If you do not agree to this, they simply take part in the current study. This information will also be destroyed after 15 years.

YOUR RELATIVES RIGHT TO LODGE A COMPLAINT WITH A SUPERVISORY AUTHORITY

Without prejudice to any other administrative or judicial remedy your relative might have, they may have the right under data protection legislation in your relatives country (where applicable) to lodge a complaint with the relevant data protection supervisory authority in their country (i.e. the Office of the Data Protection Commissioner in Ireland) if they consider that we have infringed applicable data protection legislation when processing their personal data. This means the country where they are habitually resident, where they work or where the alleged infringement took place.

CONTACT US

For further information or if you have any questions or queries about this Participant Information and Assent Form, please contact:

By letter:	Orlaith McCarthy, Data Protection Officer, St Vincent's University Hospital Elm Park, Dublin 4
By email:	dataprotection@st-vincents.ie
By telephone:	(01) 221 3591

Annex 2: List of Possible Side Effects:

Antibiotics: Diarrhea, dizziness, headache, stomach ache, tingling, nausea, vomiting, heartburn, a bad taste, swelling of mouth mucous membrane and tongue, worse sight, deafness, anorexia, itching, rash, joint pain, tiredness, phlebitis, general anaemia, arrhythmias, excessive sweating, shortness of breath, drowsiness, anxiety and confusion and nervousness;

Hydrocortisone can have the following side effects:
Water retention, nausea, increased risk of infection, high blood pressure, general malaise and hypersensitivity.

Oseltamivir can have the following side effects:
Headache, nausea, vomiting, stomach pain, diarrhoea, increased risk of infection, coughing, sore throat, general malaise and hypersensitivity.

Lopinavir/ritonavir may have the following side effects: Nausea, diarrhoea, vomiting, gastro-oesophageal reflux, pancreatitis and colitis. Hypersensitivity (including urticaria and angioedema). Skin infections or maculopapular rash, and night sweats. Anxiety, headache (including migraine), (peripheral) neuropathy, arthralgia, muscle spasms, asthenia. Hepatitis, increased levels of ALT, AST and γ-GT

Interferon beta-1a may have the following side effects: severe increase in aminotransferases, arthralgia, muscle ache/spasms, rigor, pruritus, rash, alopecia, diarrhoea, vomiting, nausea, depression, hypoesthesia.

Anakinra may have the following side effects: headache, infection, neutropenia, thrombocytopenia, raised blood cholesterol, injections site reaction, increase in hepatic enzyme action.

Hydroxychloroquine may have the following side effects: headaches, blurred vision, anorexia, cardiac disorders, gastrointestinal symptoms (vomiting diarrhoea, nausea, abdominal pain), rash, mood changes

Azithromycin may have the following effects: headache, diarrhoea, vomiting, abdominal pain, nausea, changes to blood counts (lymphocytes, monocytes, basophils, blood bicarbonate, eosinophils, neutrophils

Your doctor knows these side effects and others that may occur.

In addition to the above-mentioned side effects, even more side effects occur, which are rare (affecting less than 1%).

ST. VINCENT'S UNIVERSITY HOSPITAL
Elm Park

ASSENT FORM

PLEASE TICK YOUR RESPONSE IN THE APPROPRIATE BOX

Date approached (dd/mm/yyyy) ___/___/_____ Time (24 h, hh:mm): ___:___

Date decision (dd/mm/yyyy) ___/___/_____ Time (24h, hh:mm): ___:___

I have been asked to give permission for the following person to participate in this medicial-scientific study:

Name 0f participant: _____Date of birth (dd/mm/yyyy): __/ __/ ____

Relationship to participant:_____

Has your relative been made a "ward of court"? YES ☐ NO ☐

Has your relative gone through a legal process to give "enduring power of attorney" to somebody (to make medical decisions on his or her behalf)? YES ☐ NO ☐

Has your relative written down his or her views in a "living will"? YES ☐ NO ☐

Are you aware of any objections he or she had to being included in a medical research study? YES ☐ NO ☐

I have read and understood this Information & Assent Form: YES ☐ NO ☐

I have had the opportunity to ask questions and discuss the study: YES ☐ NO ☐

I have received satisfactory answers to all my questions: YES ☐ NO ☐

Do you have any objection to your relative taking part in the study? YES ☐ NO ☐

I have received enough information about this study: YES ☐ NO ☐

I understand that I am free to withdraw my relative from the study at any time without giving a reason and without this affecting my relative's medical care: YES ☐ NO ☐

I know that as soon as my relative is well enough, he or she will be asked whether he or she consents to be included in the study: YES ☐ NO ☐

I give informed assent to have my relative's data processed as part of this research study. YES ☐ NO ☐

STORAGE & FUTURE USE OF INFORMATION:

- I give permission for material/data to be stored for 15 years for possible future research related to the current study without further consent being required but only if the research is approved by a Research Ethics Committee.

  YES ☐ NO ☐

I give permission for participation in (please indicate a choice for each line)

		Permission	No permission	Not applicable
1	Antibiotic domain	☐	☐	☐
2	Macrolide duration domain	☐	☐	☐
3	Steroid Domain	☐	☐	☐
4	Antiviral Domain	☐	☐	☐
5	Use of COVID-19 antiviral treatment	☐	☐	☐
6	Use of COVID-19 immune modulation therapy	☐	☐	☐
7	Permission to use data from the patient's medical record	☐	☐	☐
8	Permission to contact the patient to complete the follow-up questionnaires:	☐	☐	☐

Next-of-kin signature: _____ Date: ___/____/_____
Relationship to participant: _____
Next-of-kin name in print: _____

Investigator's Signature: _____ Date: ___/____/_____
Investigator's Name in print: _____

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WITHDRAWAL FORM FOR PREVIOUSLY GIVEN CONSENT

Participation withdrawn by:

☐ patient

☐ Next-of-kin, name: _____

Relationship with patient _____

I hereby state that I withdraw (part of my) participation in the study.

This withdrawal is applicable to the following parts of the study (please indicate a choice on each line):

	Withdrawal	**No change**
Antibiotics domain	☐	☐
Macrolide domain	☐	☐
Steroid domain	☐	☐
Anitviral Domain	☐	☐
Use of COVID-19 antiviral treatment	☐	☐
Use of COVID-19 immune modulation therapy	☐	☐
Permission to use data from the patient's medical records	☐	☐
Permission to contact patient to complete the follow-up questionnaires	☐	☐

Reason for withdrawal (not mandatory): _____

Name participant: _____

Date of withdrawal (dd/mm/yyyy): ___/___/_____

Signature: